REMARKS

1. Status of the Claims

Claims 1-29 were originally filed in the present application. Claims 1-29 were canceled and claims 30-56 were added in an Amendment mailed June 23, 1998. Claims 30-56 were canceled and claims 57-60 were added in an Amendment mailed August 02, 1999. Therefore, claims 57-60 are pending in the present application. Reconsideration in view of the remarks on record and the remarks below is respectfully requested.

The claim amendments in the Response to After Final Office Action mailed on April 15, 2004 were not entered. The presently listed claims, listed hereinabove, supercede the claim amendments mailed on April 15, 2004. In order to insure that a complete submission is made in regard to the filing of an RCE under 37 C.F.R. § 1.114, the following additional remarks are provided and are directed to the Final Office Action mailed December 15, 2003 (hereinafter, the "Action").

2. Rejection of Claims 57-60 under 35 U.S.C. § 112, First Paragraph, Written Description

The Action rejected claims 57-60 under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. An applicant shows possession of the claimed invention

by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Furthermore, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

The Action reasons that an adequate written description of the claimed invention with all of its limitations is allegedly not provided by the specification because 1) there "is no description of where within the coding sequence for any of the other members of the genus of potential anchor matrix polypeptides one would insert the sequence for the linker polypeptide and the desired polypeptide", 2) the "art teaches that the process of phage morphogenesis is exceedingly complex", and 3) "it would be helpful to be able to reliably predict the functional/structural characteristics of a given fusion protein based upon its primary sequence alone".

Referring to the assertion that there "is no description of where within the coding sequence for any of the other members of the genus of potential anchor matrix polypeptides one would insert the sequence for the linker polypeptide and the desired polypeptide", Applicants respectfully submit that, for example, the protein matrix anchor "may be selected from the group consisting of any of the proteins displayed on the surface of the phage particle and comprise the head proteins pE, PD, pB, pW, pEII, pB* (pB* refers to the cleavage product of pB), pXI, and pX2 and the tail proteins pJ, V, G, M, and T" (see, e.g., page 22, lines 16-21). The claims include the limitation that the "second translatable sequence [is] operatively linked downstream to said first translatable sequence" (which first translatable sequence encodes the lambdoid bacteriophage head or tail protein). Thus, in the

present example, the claimed recombinant lambdoid vector encodes a fusion protein that comprises any of the proteins displayed on the surface of the phage particle operatively linked upstream of said second translatable sequence. Therefore, in this example, the encoded fusion protein comprises a head or tail protein operatively linked by its carboxy terminus to a linker polypeptide which is operatively linked to a preselected polypeptide. Accordingly, the assertion that there "is no description of where within the coding sequence for any of the other members of the genus of potential anchor matrix polypeptides one would insert the sequence for the linker polypeptide and the desired polypeptide" is without merit and should be withdrawn because in certain embodiments the specification teaches that the linker and preselected polypeptides are to be linked downstream of the head or tail protein.

Referring to the assertion that the "art teaches that the process of phage morphogenesis is exceedingly complex", Applicants respectfully submit that the present assertion is irrelevant in support of an alleged insufficiency in the description of the claimed invention for the following reasons. The phrase "exceedingly complex", in referring to phage morphogenesis, is an inappropriate anthropomorphic description of phage morphogenesis because phage morphogenesis is what it is. The process of phage assembly is known in the art to occur and the present specification teaches that phage assembly still occurs when a fusion polypeptide comprising the pV tail protein and a preselected polypeptide form part of the phage particle (see, e.g,. page 120, line 8 through page 122, line 30). The specification further makes the assertion that the remaining head and tail proteins (listed above) can be used in place of the pV tail protein (see, e.g., page 22, lines 16-21). The Examiner, on the other hand, does not offer any evidence that a fusion polypeptide comprising one of the other head or tail proteins and a preselected polypeptide will actually block assembly of the phage particle. The record only

offers conjecture that the said phage particles will not assemble because phage morphogenesis is said to be "exceedingly complex". The present rejection should be withdrawn because the record does not provide supported evidence that the specification has an insufficient written description of the claimed invention.

Referring to the assertion that "it would be helpful to be able to reliably predict the functional/structural characteristics of a given fusion protein based upon its primary sequence alone", Applicants respectfully submit that the present assertion is irrelevant and immaterial. It is not necessary to know the functional structural characteristics of a given fusion protein based upon its primary sequence alone in order to practice the claimed invention. Applicants demonstrated that this is not necessary by expressing a fusion polypeptide comprising the pV tail protein and a preselected polypeptide on the surface of the lambdoid phage particle without deriving the functional/structural characteristics of the fusion protein from the primary sequence alone. Applicants respectfully request that the present basis for rejection be withdrawn because it is without merit.

The Action further states at page 8, first paragraph, "The examiner does not contest that there is literal support for the limitations recited in the rejected claims". Applicants respectfully submit that there is adequate written description of the presently claimed invention because "literal support for the limitations recited in the [rejected] claims" is all that is required to meet the written description requirement. Accordingly, Applicants respectfully request that the present rejection be withdrawn because, in the Examiner's own words, "there is literal support for the limitations recited in the rejected claims".

3. Rejection of Claims 57-60 under 35 U.S.C. § 112, First Paragraph, Enablement

The Action rejected claims 57-60 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a recombinant lambdoid bacteriophage vector or bacteriophage comprising fusions with lambdoid bacteriophage tail polypeptides that are pV, allegedly does not reasonably provide enablement for embodiments wherein the lambdoid phage anchor matrix protein is other than pV. The present rejection is respectfully traversed for the reasons of record and the reasons discussed below.

The test of enablement is whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Wands factors are reviewed in the Action and Applicant's remarks regarding the Wands analysis are provided below.

A. Nature of the Invention

The Action states that the "nature of the invention is complex". Applicant respectfully submits that the Examiner is assigning an inappropriate anthropomorphic term ("complex")to the process of phage assembly. Phage assembly is known to occur in the art and the present specification teaches that phage assembly occurs in the presence of a pV tail protein fusion polypeptide (see above). The specification further asserts which other head and tail proteins can be used to form a fusion with a preselected polypeptide and still arrive at a functional recombinant lambdoid bacteriophage vector (see above). The

Examiner has offered no evidence, only conjecture about the "complex" nature of phage assembly, on the record that the claimed recombinant lambdoid bacteriophage vector includes non functional species.

B. Breadth of the Claims

The Action asserts that the "breadth of the claims, encompassing any of the proteins displayed on the surface of the phage particle (e.g., head proteins: pE, pD, pW, pFII, pB*, pX1, pX2; tail proteins: pV, pJ, pG, pM, and pT; page 22 lines 13-21), greatly increases the complexity of the invention". Applicants respectfully submit that the specification teaches or asserts that any of the head or tail proteins can be used in the claimed invention. However, the Examiner has failed to provide evidence that species within the claimed invention are not functional as claimed. The Examiner has provided on the record only conjecture that the invention will not function as claimed because phage assembly is "complex".

C. Guidance of the Specification/The Existence of Working Examples

The Action asserts that the "specification provides specific guidance and working examples only for the major tail protein pV and the prior art is silent on fusion proteins that include the other tail proteins or head proteins of lambdoid phage". Applicants respectfully submit that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed (MPEP 8EdR2, 2164.02). Still, the specification does provide a working example of the claimed invention and asserts that the other surface expressed head or tail proteins can be likewise cloned into the same vector used in the working example to arrive at the claimed recombinant lambdoid bacteriophage vector. The Examiner has provided no evidence that the demonstrated or asserted fusion polypeptides of the specification will not assemble into lambdoid phage particles. The

Examiner has only provided conjecture that because phage assembly is allegedly "complex" the claimed invention might not be achieved for fusion polypeptides comprising a head or tail protein other than pV tail protein.

D. State of the Art

The Action asserts that the "state of the art at the time of applicants' invention was high, requiring a high degree of skill in order to make and use the claimed invention". Applicants respectfully submit that one of skill in the art at the time the application was filed typically had an advanced degree and/or experience in the relevant art and; thus, possessed the "high degree of skill in order to make and use the claimed invention" in view of the disclosures in the specification.

The Action further asserts that "There is no guidance within the prior art as to which particular nucleotide sequences within the gene encoding any potential matrix anchor protein are suitable for insertion of a heterologous coding sequence such that the expressed fusion protein from such a construct will not disrupt particle assembly and will allow functional, accessible display of the desired preselected polypeptide on the mature phage particle". Applicants respectfully submit that the guidance for making a gene fusion for expression of a fusion polypeptide comprising a head or tail protein and a preselected polypeptide is provided in the specification, for example, at page 22, lines 13-21 and at page 120, line 8 through page 122, line 30. The Examiner has not provided any evidence that the claimed recombinant lambdoid bacteriophage vector cannot express the preselected polypeptide on the surface of the phage.

E. Predictability of the Art

The Action asserts that "the art of predicting how a particular protein will fold to form the structure which provides its

functionality is not exact ... because the relationship between the sequence of a protein and its tertiary structure ... is not well understood and is not predictable"; therefore, implying that the claimed invention is unpredictable. Applicants respectfully submit that the claims do not include a limitation of predicting protein structure from the sequence of a protein. Therefore, the present assertion is irrelevant and immaterial because the claims to not recite the alleged unpredictable limitations and because the specification teaches the claimed invention in a working example without the need for predicting tertiary protein structure from the primary sequence.

The Action further asserts "that the first envisioned modification of a lambda phage head or tail protein to include a heterologous sequence would not be successful because one cannot predict a priori the final structure and functional characteristics of the fusion protein based upon primary sequence alone". Applicants respectfully point to the teachings of the specification wherein a first lambdoid phage head or tail protein (pV) is modified to further comprise a preselected polypeptide and the preselected polypeptide is found to be expressed on the surface of the phage and to be functional (see, e.g., page 120, line 8 through page 126, line 21). Accordingly, the present assertion that the first envisioned modification would not be successful is without merit because the specification provides a working example of at least one envisioned embodiment.

The Action next asserts that Applicants' own teachings of the "successful incorporation into a mature tail of pV protein fusions is <u>somewhat</u> unpredictable" because "the plaques were smaller in su^+ hosts" and because "phage tails displaying beta-galactosidase contained only one to a few copies of the fusion polypeptide" (emphasis added). Applicants respectfully submit that it is irrelevant that the plaques (comprising a pV fusion polypeptide) were smaller or that the copy number of the fusion polypeptide was less than the total

number of pV polypeptides present in the phage because, in fact, the pV fusion polypeptide was displayed and it was functional as taught by the specification and because there is no claim limitation directed to plaque size or copy number.

The Action next asserts that "The successful incorporation into the tail of altered forms of one of the tail proteins (e.g. pV) does not provide evidence that any of the other matrix proteins (head or tail proteins) can be similarly modified without impairing their unique role in phage assembly (emphasis added). As discussed above, the specification teaches that a fusion polypeptide comprising pV and a preselected polypeptide provides a functional expression of the preselected polypeptide on the surface of the phage particle. Also, as discussed above, the specification asserts that any lambdoid phage head or tail protein can be substituted for the pV protein in the fusion polypeptide to arrive at a functional expression of the preselected polypeptide on the phage surface. Applicants respectfully submit that it is the Patent Office that bears the initial burden of presenting evidence of a *prima facie* case of lack of enablement. Until the Patent Office establishes a prima facie case of lack of enablement of the claimed invention, Applicants cannot be required to submit additional evidence that the "other matrix proteins (head or tail proteins) can be similarly modified without impairing their unique role in phage assembly". Furthermore, it is not enough for the Patent Office to establish that modification of the head or tail proteins impairs their role in phage assembly, Applicants respectfully submit that the Patent Office must establish by supported evidence or supported reasoning that said modification eliminates surface expression of a functional preselected polypeptide on the phage surface.

The Action next asserts that the Applicants submission of Mikawa et al. as evidence of enablement for other capsid or tail proteins (other than pV) is not relevant because the teachings of Mikawa et al.

are allegedly not commensurate with the teachings of the instant disclosure. Applicants rely on the remarks entered into the record in the Response dated September 12, 2003 that Mikawa et al. teaches virtually the identical procedure for expression of a phage using the pD protein as that taught in the instant specification including the use of the λfoo vector for making the claimed recombinant lambdoid bacteriophage vector. In addition, Mikawa et al. teaches that "gpD may be fused to many other peptides and proteins at their N or C terminus and the fusion products may be accessible on the surface of bacteriophage λ particles". Thus, Mikawa et al. provides proof that the teachings of the instant application enable one of ordinary skill in the art to make and use the claimed invention. Further, given that pV is a tail protein and the pD is a head protein, this evidence, in Mikawa et al., provides explicit support that the teachings of the instant specification enable the claimed invention for both head and tail proteins.

The Action further asserts that allegedly there is no teaching or working example in the instant specification that indicates where in the coding sequence of any other potential matrix anchor protein (with the exception of pV) it is appropriate to insert coding sequences for the linker polypeptide and the preselected protein. As discussed above in the written description section, the specification discloses certain embodiments wherein the encoded fusion protein comprises a head or tail protein operatively linked by its carboxy terminus to a linker polypeptide which is operatively linked to a preselected polypeptide (see above and, e.g., page 22, lines 16-21).

F. The Amount of Experimentation Necessary

The Action asserts that the claimed invention would allegedly require undue experimentation to make even one embodiment of the claimed invention not involving pV as the matrix anchor protein. Applicants respectfully traverse the present assertion because the

specification teaches a working example involving pV as the matrix anchor protein and asserts that any of the head or tail proteins expressed at the surface of the lambdoid phage can be used in place of pV. Thus, the specification teaches the entire breadth of the claims.

The Action asserts that "One would first have to envision an appropriate matrix anchor protein construct in which the coding sequence for the matrix anchor protein is operatively linked at a particular sequence with the coding sequences for a linker polypeptide and desired, preselected polypeptide, make the construct and express the hybrid gene during morphogenesis such that the fusion protein might be incorporated into the phage particle and then determine whether functional phage particles are formed which display the desired, preselected polypeptide sequence in an accessible and/or functional manner". Applicants respectfully submit that the specification teaches each of the above recited steps, for example, at page 22, lines 13-21, and at page 120, line 8 through page 126, line 21.

The Action further implies that if the expression of a functional preselected polypeptide on the surface of the phage is unsuccessful, and that such expression is allegedly likely to be unsuccessful, then one skilled in the art is allegedly faced with undue experimentation to practice the claimed invention. Applicants respectfully submit that the specification asserts that incorporation of the linker and preselected polypeptide downstream of the head or tail protein, in the claimed vector, results in the surface expression of a functional preselected polypeptide on the lambdoid bacteriophage particle. The Examiner's assertion that the expression is allegedly likely to be unsuccessful is unsubstantiated speculation of the result of an experiment that in all instances in which it was performed (using pV in the instant specification and using pD in Mikawa et al.) had a successful result of surface expression of a functional preselected polypeptide on the surface of the lambdoid phage.

The Examiner asserts that surface expression of a functional preselected polypeptide on a lambdoid phage is allegedly likely to be unsuccessful because of the "lack of guidance from the specification or the prior art as to which portions of the other potential matrix anchor proteins are dispensable for particle assembly and [because of] the unpredictability of the art as evidences by applicants' own teaching regarding pV". Again, Applicants respectfully submit that the specification asserts that incorporation of the linker and preselected polypeptide downstream of the head or tail protein, in the claimed vector, results in the surface expression of a functional preselected polypeptide on the lambdoid bacteriophage particle; thus, the specification does provide guidance as to where to insert the respective proteins in the vector. Also, Applicants respectfully submit that the teachings in the specification regarding pV cannot be interpreted to indicate "unpredictability of the art" because a functional preselected polypeptide was expressed on the surface of the lambdoid bacteriophage. It is irrelevant that the plaque size was reduced compared to wild-type plaques and that the copy number of the preselected polypeptide was less than the copy number of the wild-type pV polypeptide in each phage particle because these are not limitations of the claims.

In view of the remarks made on the record and the remarks made hereinabove, Applicants respectfully request that the present rejection be withdrawn because the specification teaches the full breadth of the claims and because the Examiner has failed to support a *prima facie* case of lack of enablement of the claims.

CONCLUSION

The Applicant respectfully requests that the Examiner enter the response herein, withdraw all claim rejections, and place the claims in condition for allowance.

The Examiner is requested to contact the representative for the Applicants, to discuss any questions or for clarification. If there are any further fees associated with this response, the Director is authorized to charge our Deposit Account No. 19-0962.

Respectfully submitted,

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Date

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